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09/724,898	11/28/2000	Leroy Hood	P-IS 4403	7808

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EXAMINER
ZEMAN, MARY K

ART UNIT	PAPER NUMBER
1631	

DATE MAILED: 07/03/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/724,898	Applicant(s) HOOD ET AL.	
	Examiner Mary K Zeman	Art Unit 1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 April 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-143* is/are pending in the application.

4a) Of the above claim(s) *17-64, 135-137, 140, 142 and 143* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16,65-134,138,139 and 141* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6 7 10* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 1-143 are pending in this application.

Applicant's election with traverse of Group IV, claims 65-134 in Paper No. 9 is acknowledged. The traversal is on the ground(s) that the claims of Group I are substantially coextensive in scope, and would not pose an undue burden upon the examiner. No arguments are presented with regards to the other groups. Applicant's arguments with regard to Group I are persuasive, and Groups I and IV are examined therein. However, the requirement is maintained with respect to the remaining groups.

The requirement is still deemed proper and is therefore made FINAL.

Claims 17-64, 135-137, 140, 142 and 143 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 9.

Claims 1-16, 65-134, 138, 139 and 141 are under examination.

Priority

Priority to two separate provisional applications under 35 USC 119(e) is acknowledged.

Information Disclosure Statement

The IDS papers filed 10/15/01, 2/20/02 and 4/17/03 have each been entered and considered. Initialed copies of the forms PTO-1449 are included with this action.

Drawings

The drawings of record are acceptable to the examiner.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-16, 65-134, 138, 139 and 141 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In *In re Wands* (8 USPQ2d 1400 (CAFC 1988)) the CAFC considered the issue of enablement in molecular biology. The CAFC summarized eight factors to be considered in a determination of "undue experimentation". These factors include: (a) the quantity of experimentation necessary; (b) the amount of direction or guidance presented; (c) the presence or absence of working examples; (d) the nature of the invention; (e) the state of the prior art; (f) the relative skill of those in the art; (g) the predictability of the art; and (h) the breadth of the claims.

In considering the factors for the instant claims:

a) In order to practice the claimed invention one of skill in the art must be able to determine what expression levels of what genes are relevant to a given health state, what levels are relevant to a disease state, what genes to study for a given health state, and statistically significant amounts of data regarding the expression levels of the genes in varying populations which would reasonably correlate with those to be tested. For the reasons discussed below, undue experimentation is required to practice the claimed invention.

b) The specification provides guidance for generic methods of determining expression levels of an array of genes. The specification also provides methods of generating multidimensional coordinate points that are representative of the expression levels, and methods of comparing the points that are generated.

c) The specification provides no working examples of diagnosing a health state, or diagnosing a particular disease using the claimed methods. The specification provides no sets of data that identify any particular genes that are to be used in any of the methods for the diagnosis of any particular health states or diseases. No sets of data which represent normal health states are set forth. No genes are identified that are representative of health. No sets of data representing genes to be studied or tested in diabetes or cancer are set forth. Diabetes and cancer are specifically recited in dependent claims. No data regarding any sorts of normalization to be done for differing population types (youth, age, gender, environment, family history, race, etc) is set forth in the specification, or claims.

d) The invention is drawn to generic methods of diagnosing or determining a health state based upon comparative expression profiling, and systems and software therefor.

e) The effective filing data and date of invention for this application is the date of the earliest file provisional application, 7/2000. At the time of the invention, and up until today, expression profiling remains a data intensive and difficult venture, even when relevant genes and expression levels are known. For example, Cole et al. (Nature Genetics Supplement 1999, vol 21 pages 38-41) discusses expression profiling in the context of cancer diagnosis. Cole documents the many challenges present in the identification of relevant genes, expression levels, samples, and analysis even for a single type of cancer, prostate cancer. Cole details the difficulties in selecting what the "normal" prostate tissue is to be considered- in a healthy prostate the "normal" epithelial duct tissues have a wide variety of phenotypes at the visual level and gene expression level, yet they are each considered normal. Cole discusses how factors of degree of associated inflammation, or proximity to other anatomical structures can influence the various tests. Cole notes that want may appear abnormal using one standard, may actually be quite normal under another, and may still be completely unrelated to disease state or progression. Cole notes that "little is known of the genes or pathways that mediate the formation or progression of prostate tumors..." which is an indication that such information was not readily available at the time of filing. Cole indicates that several hundred adjacent slices of a tissue sample are needed for the analysis disclosed. Cole discusses many of the difficulties and questions that must be addressed in microarray based experiments, including small sample amounts, amplification bias, target bias, and reproducibility. Finally, Cole charts out future work that is needed to identify and analyze the information generated by these experiments.

In a review by Neil Risch published in June of 2000, (Risch, N.J. Nature 15 June 2000 Vol. 405, pages 747-856) the extreme difficulties faced by biologists in identifying genes linked to a variety of complex non-mendelian disorders. Despite the sequencing of the human genome, Risch notes that "the promise of the same technology (Mendelian genetics) solving the problem of more frequent, non-mendelian familial disorders has largely been unfulfilled." Risch reviews the several known methods for linking genes to disorders (case-control studies, linkage analysis, positional cloning, genetic heterogeneity, etc) and how these studies fail in complex diseases that are multifactorial in nature. Risch discusses the intensive level of work, discovery and invention

that is required to identify genes associated with many diseases. He notes that "efficient study designs will still be required, and multiplex families, the mainstay of linkage based studies will still be optimal. However, instead of family-based controls, unrelated controls will emerge as a more powerful and efficient approach (especially for analyses based on pooled DNA samples) and robustness will be maintained by studying a large number of independent SNP's. Sampling families of varying ethnicity will also be advantageous from the perspective of enhancing evidence of causality as well as identifying genetic and/or environmental factors." Clearly this indicates that none of the data was readily available to one of skill in the art at the time the invention was made, and that the gathering and analysis of the information requires great inventive work and decision making on the part of the skilled artisan.

In a related review in the same issue, Lockhart and Winzeler discuss comparative expression profiling, and the state of this art as of June 2000. (Lockhart, D.J. et al. Nature 15 June 2000, vol. 405 pages 827-836) They note that the technical aspects of performing microarray experiments have largely been made routine. What is not routine is the selection of the genes to be used in the comparative profile for any given condition. Lockhart discusses a study of B-cell lymphoma patients wherein samples from patients and healthy controls were studied using microarray experiments. After considerable effort, a set of genes were identified which can be used in the classification of certain subtypes of B-cell lymphoma samples. Lockhart states that it is important to monitor large numbers of genes, both disease associated and normal. Lockhart reviews how gene expression profiling technology could be used for classification, diagnosis, or target validation but indicates that large amounts of data are still required. Finally, Lockhart discusses the difficulties in the analysis of the results of such assays. He indicates that a great deal of dedicated, systematic human effort will be required to end up with answers and analyses that are scientifically rigorous, statistically significant, and useful to the scientific and/or medical community. The requirements for such effort clearly is an indication that a large amount of inventive discovery and work would be required to make comparative expression profiling for diagnosis doable and useful.

In the same issue of Nature, a review by Roses (Roses, A.D. Nature 15 June 2000 pages 857-865) tackles the issues of pharmacogenomics, including comparative expression profiling for disease diagnosis. Roses concentrates on SNP mapping and typing, which is different than

measuring expression levels of genes, but has similar requirements for knowledge of what genes to study for the diagnosis of particular diseases. Roses discusses the issues of ApoE profiling in Alzheimer's disease. Multiple polymorphisms of this gene have been identified, some of which are associated with disease, some of which are not. Further, the disease appears to be influence by multiple genes, both in a causal and protective manner. Roses notes that there is no large body of knowledge from which to draw to readily identify genes which are associated with complex, non-mendelian disorders.

In an article by Moler et al. is an example of the intensive, inventive work required to identifyi genes and gene sets which are relevant to a given disorder, even using sophisticated technology. Moler et al. (Moler, E.J. et al. Physiol. Genomics December, 2000, Vol. 4 pages 109-126) discuss colon adenocarcinoma gene expression profiles, and use baysian network analysis to classify the expression profiles into one of three classes or subtypes. Nearly 2000 genes were identified and cataloged for each classification, subtype and sample. 62 different samples were used, and ultimately about 90 genes were identified as being marker genes for the classification of colon adenicarcinoma. Such intensive work and effort would be required for every conceivable health state, disease, disease progression etc.

f) The skill of those in the art of molecular biology and bioinformatics is high.

g) The prior art predicts that a great deal of dedicated, systematic human effort will be required to end up with answers and analyses of gene expression profiling that are scientifically rigorous, statistically significant, and useful to the scientific and/or medical community.

h) The claims are broad because they are drawn to generic methods of diagnosing or determining a health state based upon comparative expression profiling, and systems and software therefore. The skilled practitioner would first turn to the instant specification for guidance to practice these methods and to create such software and systems. However, the instant specification does not provide specific guidance to practice these embodiments. As such, the skilled practitioner would turn to the prior art for such guidance, however, the prior art shows that a great deal of dedicated, systematic human effort will be required to end up with answers and analyses of gene expression profiling that are scientifically rigorous, statistically significant, and useful to the scientific and/or medical community. Finally, said practitioner would turn to trial and error experimentation to determine what expression levels of what genes are relevant to

a given health state, what levels are relevant to a disease state, what genes to study for a given health state, and statistically significant amounts of data regarding the expression levels of the genes in varying populations which would reasonably correlate with those to be tested.. Such represents undue experimentation.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-16, 65-134, 138, 139 and 141 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In the independent claims (1, 65, 81, 90, 105, 138, 141) the metes and bounds of the steps set forth are unclear. Steps such as "comparing" and "determining" without concrete, specific limitations as to how they are to be performed are not descriptive of the method intended to be claimed.

In all the dependent claims (claim 2 for example) it is unclear where in the independent method the further limitation should be placed. At what point in the method of claim 1 should the expression levels be input? To what should they be input? Claim 1 does not require a computer, database, input system etc. The way that claim 2 reads, it would appear one is to input the levels into the sample, however this does not make sense.

Further, it would appear that the limitations of claim 2 must already be done or known before the method of claim 1 can even be performed, such that this limitation appears meaningless. Similar issues exist for claim 3. One would have to determine the expression levels in order to determine the multipoint coordinate representing those levels.

In claim 5, at what point in the method of claim 1 or 3 is the sample contacted with the target? At the beginning? At the end? What is the target? A drug? An array? How does this influence the performance of the underlying method?

In claim 65, the steps of the method do not meet the goal of the preamble. Following the steps of the method, one determines whether a health state or a disease state is present. This is not strictly the same as diagnosis of a disease. Diagnosis of a disease usually combines

biological tests with symptom assessment, patient assessment. A single test result rarely is enough for the diagnosis of a disease.

In regards to claim 66, at what point in the method of claim 65 should the expression levels be input? To what should they be input? Claim 65 does not require a computer, database, input system etc. The way that claim 66 reads, it would appear one is to input the levels into the sample, however this does not make sense.

Further, it would appear that the limitations of claim 66 must already be done or known before the method of claim 65 can even be performed, such that this limitation appears meaningless. Similar issues exist for claim 67. One would have to determine the expression levels in order to determine the multipoint coordinate representing those levels.

In claim 69, at what point in the method of claim 65 or 67 is the sample contacted with the target? At the beginning? At the end? What is the target? A drug? An array? How does this influence the performance of the underlying method?

In claim 81, the steps of the method do not meet the goal of the preamble. Following the steps of the method, one determines whether a health state or a disease state is present. This is not strictly the same as diagnosis of a disease. Diagnosis of a disease usually combines biological tests with symptom assessment, patient assessment. A single test result rarely is enough for the diagnosis of a disease.

In regards to claim 91, at what point in the method of claim 90 should the expression levels be input? To what should they be input? Claim 90 does not require a computer, database, input system etc. The way that claim 91 reads, it would appear one is to input the levels into the sample, however this does not make sense.

Further, it would appear that the limitations of claim 91 must already be done or known before the method of claim 90 can even be performed, such that this limitation appears meaningless. Similar issues exist for claim 92. One would have to determine the expression levels in order to determine the multipoint coordinate representing those levels.

In claim 94, at what point in the method of claim 90 or 92 is the sample contacted with the target? At the beginning? At the end? What is the target? A drug? An array? How does this influence the performance of the underlying method?

In claim 106, why is the method performed multiple times? How does that affect the determination of a health state? Is it repeated on the same sample? Different samples? Samples from the same person over time? Different people? If it is done on the same sample, are the same gene profiles obtained? Are differing health states being assessed? None of these questions are answered by the claims.

In regards to claim 124, at what point in the method of claim 105 should the expression levels be input? To what should they be input? Claim 105 does not require a computer, database, input system etc. The way that claim 124 reads, it would appear one is to input the levels into the sample, however this does not make sense.

Further, it would appear that the limitations of claim 124 must already be done or known before the method of claim 105 can even be performed, such that this limitation appears meaningless. Similar issues exist for claim 125. One would have to determine the expression levels in order to determine the multipoint coordinate representing those levels.

In claim 127, at what point in the method of claim 105 or 125 is the sample contacted with the target? At the beginning? At the end? What is the target? A drug? An array? How does this influence the performance of the underlying method?

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the

reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 1-16, 65-134, 138, 139 and 141 are rejected under 35 U.S.C. 102(e) as being anticipated by Friend et al. (US 6,324,479 B1).

The claims are drawn to methods of diagnosis of a health state or disease using comparative expression profiling. An expression profile of a sample is obtained, manipulated and compared to reference expression profiles. A profile or manipulated profile that does not fall within a region determined to be "normal" is identified as a perturbed health state or as a disease state. The sample can be blood, serum or leukocytes, the samples can be applied to an array. DNA, proteins, or small molecules can be used to generate the expression profile. Computer systems and software for performing the methods are claimed.

Friend et al. (US Patent 6,324,479 B1 having priority to at least April 1999) disclose methods of comparative expression profiling for the diagnosis of a health state or disease. Profiles of a sample are taken and compared to reference profiles. Nucleic acids, proteins or small molecules can be measured for the profiles. A profile that deviates from the normal or expected profile is classified as a perturbed profile, which can be further correlated to a health state or disease. A variety of biological samples are contemplated including blood, serum, tissue, etc. Computer systems and software for carrying out the methods are described. As such, this disclosure meets the limitations of the claims.

Claims 1-16, 65-134, 138, 139 and 141 are rejected under 35 U.S.C. 102(e) as being anticipated by Friend et al. (US 2001/0018182 A1).

Friend et al. (US Patent 2001/0018182 A1 having priority to at least June 1999) disclose methods of comparative expression profiling for the diagnosis of a health state or disease. Profiles of a sample are taken and compared to reference profiles. Nucleic acids, proteins or small molecules can be measured for the profiles. A profile that deviates from the normal or expected profile is classified as a perturbed profile, which can be further correlated to a health state or disease. A variety of biological samples are contemplated including blood, serum, tissue, etc. Computer systems and software for carrying out the methods are described. As such, this disclosure meets the limitations of the claims.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mary K Zeman whose telephone number is (703) 305-7133.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, can be reached at (703) 308-4028.

Official fax numbers for this Art Unit are: (703) 308-4242, (703) 872-9306. An *unofficial* fax number, direct to the Examiner is (703) 746 5279. Please call prior to use of this number.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the TC1600 Receptionist whose telephone number is (703) 308-0196.

mkz
6/27/03

MARY K. ZEMAN
PRIMARY EXAMINER
AU 1631